Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study

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Concurrent and Adjuvant Temozolomide for 1p/19q non-co-deleted anaplastic glioma: interim results of the randomized intergroup CATNON trial (EORTC study 26053-22054).

Running title: Interim analysis of the CATNON trial, a report of the EORTC Brain Tumor Group

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Research in context

Evidence before this study

At the time of study initiation, past studies on PCV chemotherapy given after radiotherapy had failed to produce survival benefit in anaplastic oligodendrogliomas which was assumed to be a chemotherapy responsive disease. These studies also showed that 1p19q non-co-deleted tumors have a much worse prognosis compared to 1p/19q co-deleted tumors. At the same time, combined chemo-irradiation with temozolomide was shown to improve outcome in glioblastoma, which was considered a relatively chemo-therapy resistant disease. In this latter study, MGMT gene promoter methylation was found to be predictive of benefit to temozolomide; it remained unclear if both temozolomide given concurrent with and after (‘adjuvant’) radiotherapy were required to improve patient outcome.

Added value of this study

In a preplanned interim analysis this study shows that 12 cycles of adjuvant temozolomide given after radiotherapy improve overall and progression free survival in non-1p/19-codeleted anaplastic glioma.

Implications of all the available evidence

Standard of post-care for non-1p/19q1 codeleted anaplastic glioma should now be surgery followed by radiotherapy and 12 cycles of standard day 1-5 every 4 weeks temozolomide. Ongoing molecular research within this trial will show whether IDH mutational status and MGMT promoter methylation can be used to identify the patients benefitting from temozolomide chemotherapy. Further follow-up of the CATNON trial is necessary to understand if temozolomide given concurrently with radiotherapy also improves survival.

Abstract Background, Methods, Findings, Interpretation, and Funding

Background

The role of temozolomide chemotherapy in newly-diagnosed anaplastic glioma without 1p/19q co-deletion ('non-co-deleted') is unclear. The CATNON trial investigated the addition of a) concurrent and b) adjuvant temozolomide chemotherapy to 59.4 Gy of radiotherapy in adult patients with non-codeleted anaplastic glioma .

Methods

In an open label study with a 2x2 factorial design patients with newly diagnosed non-co-deleted anaplastic glioma were randomized using minimization technique to either radiotherapy alone, radiotherapy followed by 12 cycles of adjuvant temozolomide 150-200 mg/m^2 day 1-5 4-weekly, radiotherapy given concurrent with daily temozolomide 75 mg/m^2, or radiotherapy with both concurrent and adjuvant temozolomide. Patients were stratified for prognostic factors including centrally assessed O-6-methylguanine-DNA methyltransferase gene promoter methylation status. The primary endpoint was overall survival (OS) adjusted for stratification factors. The study design required 748 patients, with a planned interim analysis once 41% (219) of the required events had occurred and which required a p-value < 0.0084 to reject the null hypothesis. (NCT00626990, EORTC 26053-22054).

Findings

745 patients were included in the interim analysis. The hazard ratio for OS for use of adjuvant temozolomide was 0.65 (99.145 % confidence interval: 0.45, 0.93) prompting the Independent Data Monitoring Committee to recommend early release of the data on adjuvant treatment. OS at 5 years was 55.9% with and 44.1% without adjuvant temozolomide.. Toxicity was mainly hematological and reversible.

Interpretation

This is the first study to show a survival benefit of temozolomide chemotherapy after radiotherapy in newly diagnosed non-co-deleted anaplastic glioma. Further follow-up is required for analysis of the role of concurrent temozolomide and of molecular factors, in particular *isocitrate dehydrogenase* gene mutations.

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Schering Plough/MSD supported this trial with an unrestricted grant and provided temozolomide; the trial was further supported by grants from the EORTC Cancer Research Fund, NRG Oncology Operations, NRG Oncology SDMC, and Cancer Australia.

Introduction

The pivotal EORTC trial combining temozolomide with radiotherapy in glioblastoma was the first to show a statistically significant and clinically meaningful benefit from adding chemotherapy to radiotherapy in glioma.1 That study also identified O6-ethylguaninemethyltransferase (MGMT) gene promoter methylation as a biomarker for increased activity of temozolomide.2 Concurrently, two trials in anaplastic oligodendroglioma investigating adjuvant chemotherapy with procarbazine, CCNU and vincristine (PCV) with radiotherapy failed to show a survival benefit at the time of their first analysis.3;4 However, these trials showed a major prognostic effect of the deletion of both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q), now known as 1p/19q co-deletion ('co-deleted') and associated previously with increased sensitivity to chemotherapy.5 Since tumors without 1p/19q co-deletion are generally less chemo-responsive, we asked whether combined chemo-radiotherapy with temozolomide would improve outcomes in non-co-deleted anaplastic gliomas, and also whether it was the concomitant (given during radiotherapy), or the adjuvant (given after conclusion of radiotherapy) temozolomide treatment which determined any survival benefit. These questions induced a trial which in a 2 x 2 factorial design randomized patients with non-co-deleted anaplastic glioma to four study arms: radiotherapy with or without concurrent temozolomide, and with or without adjuvant temozolomide. Shortly after the end of accrual a planned interim analysis was conducted. This analysis resulted in the recommendation by the Independent Data Monitoring Committee (IDMC) to immediately release the data on the addition of adjuvant temozolomide to radiotherapy. We now report on the outcome of adjuvant treatment based on the data and events the IDMC reviewed.

Methods

The CATNON intergroup trial was conducted in Australia (Cooperative trials Group for Neuro-Oncology, COGNO), North America (NRG Oncology, Canadian Clinical Trials Group (CCTG) and Europe

(European Organization for Research and Treatment of Cancer (EORTC), Medical Research Council (MRC), NeuroOnkologische Arbeitsgemeinschaft der Deutschen Krebsgesellschaft (NOA)).

Study design and participants

The trial was a phase III, randomized, open-label, 2 x 2 factorial study involving patients with newly diagnosed anaplastic glioma without 1p/19q co-deletion. Previous surgery for low grade glioma was allowed, provided histological confirmation of an anaplastic tumor was obtained at progression. Patients were 18 years or older, with a WHO performance status 0-2, adequate hematological, renal and liver function, and on a stable or decreasing dose of corticosteroids. Treatment with other experimental agents was not allowed. Patients were required to start radiotherapy within 7 weeks of surgery and within 8 days of randomization. All patients gave written informed consent according to local, national and international guidelines. After stratification for institution, performance status (0 vs >0), age (≤50 vs >50 years of age), 1p loss (yes vs no), the presence of oligodendroglial elements at microscopy (yes vs no) and MGMT promoter methylation status (methylated vs unmethylated vs indeterminate) patients were electronically randomized through the EORTC web-based ORTA system (http://www.eortc.org/investigators/).

Tumor evaluation

At patient registration, tumor material was submitted for pathology review, 1p/19q status determination, and assessment of MGMT promoter methylation status. Pathology review and central 1p/19q determination were performed separately for North American and European/Australian patients. After central review of their local 1p/19q testing procedure, dedicated and experienced European centers were allowed to enroll patients based on the local histological and molecular diagnosis. For patients from centers requiring central pathology review, confirmation of the diagnosis of anaplastic glioma was required. For Europe and Australia, 1p/19q status was assessed using microsatellite analysis; in North America 1p/19q diagnostics were done with fluorescent in situ hybridization (FISH).[6;7] MGMT promoter methylation was performed by two central laboratories using quantitative PCR as previously described.[8] If MGMT determination was not available in time to meet radiotherapy timelines, patients were randomized with an ‘indeterminate’ MGMT methylation status.

Treatment

Patients were 1:1:1:1 randomized using the minimization technique to radiotherapy alone, radiotherapy combined with temozolomide, radiotherapy followed by temozolomide, or radiotherapy combined with and followed by temozolomide. Radiotherapy consisted of 59.4 Gy in 33 fractions of 1.8 Gy. Whenever possible, target volume definition was based on co-registered pre- or (ideally) post-operative magnetic resonance imaging (MRI). From 2011 onwards, centers were allowed to use IMRT after additional quality assurance. The radiotherapy gross tumor volume (GTV) volume was the entire region of high signal intensity on T2 weighted MRI images or FLAIR sequences, the regions of enhancement, and the tumor resection cavity. A 1.5 to 2.0cm margin (edited for anatomical barriers) was added to the GTV for microscopic spread, and then 0.5-0.7cm for daily set-up variability. Planning could be either by 3D-conformal radiotherapy or IMRT and the plan had to conform to the ICRU 50/62 criteria for target volume coverage, dose normalization and homogeneity.[9;10] Temozolomide was given daily during radiotherapy (including on non-radiotherapy weekend days) at a dose of 75 mg/m2 for a maximum of 7 weeks. Adjuvant temozolomide started four weeks after completion of radiotherapy, for a maximum of 12 planned cycles. Temozolomide was given on days 1-5 every four weeks at a dose of 150 mg/m2 during the first cycle with dose escalation to 200 mg/m2 for subsequent cycles if no or only minimal toxicity was observed during the first cycle. Dose modifications were made as described elsewhere.[1] Treatment at progression was left to the discretion of the treating physicians, but temozolomide was suggested in patients randomized to radiotherapy only. During concomitant chemo-radiotherapy, pneumocystis jirovecii prophylaxis was mandatory.

Assessments

Patients were reviewed weekly during radiotherapy, four-weekly during adjuvant temozolomide treatment and every three months after the completion of all therapy. Radiological assessment used MRI scans at baseline, four weeks after the end of radiotherapy and thereafter every three months until progression. Following progression, patients were followed up for survival. Progression was assessed using Macdonald's criteria, incorporating steroid dose and with a description of the possibility of pseudoprogression.11 For non-enhancing tumors, progression was defined as a 25% increase in tumor area defined as the product of the two largest perpendicular diameters. Toxicities were scored using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 3.0. For health-related quality of life (HRQoL) analysis, the EORTC QLQ-C30 and BN20 questionnaires were used at baseline and all visits corresponding to MRI imaging.12 Cognition was assessed at the same time points using the MiniMental State Examination, and in dedicated centers with a more comprehensive test battery which was performed annually after the start of radiotherapy.13;14 HRQoL and Cognitive assessments will be reported separately.

Statistics

The study used a 2 by 2 factorial design with overall survival (OS) adjusted by the stratification factors as the primary endpoint. The study intended to answer two questions:

QI: whether OS would be improved by concurrent temozolomide chemotherapy (comparing all patients receiving radiotherapy alone or radiotherapy followed by adjuvant temozolomide to all those receiving either radiotherapy and concurrent temozolomide or radiotherapy and concurrent followed by adjuvant temozolomide)

QII: whether OS would be improved by adjuvant temozolomide chemotherapy (comparing all patients receiving radiotherapy alone and radiotherapy with concurrent temozolomide to all those receiving radiotherapy followed by adjuvant temozolomide or radiotherapy and concurrent followed by adjuvant temozolomide)

Survival was calculated from the date of randomization to the date of death from any cause. Secondary endpoints included univariate OS, PFS adjusted for stratification factors, landmark OS and PFS analyses, HRQoL outcomes, toxicity, and cognition. PFS was defined as the time from randomization to the date of first progression or death, whichever came first. For all time to event analyses, patients still alive and not having met the endpoint at the last follow-up visit were censored. The Kaplan Meier technique was used for the univariate estimates of OS and PFS. For the primary analysis of OS and PFS, the Cox proportional hazards model was fit with a question indicator variable (one for each question, QI and QII). Assuming a median survival of 24 months in patients receiving radiotherapy only and a risk reduction of 0.775 for both concurrent temozolomide and adjuvant temozolomide (two-sided logrank test), at an overall significance level of 5% and a power of 83%, 523 events were needed and 748 patients were to be recruited. One interim analysis for efficacy was planned when 41% of the required events (n=219) had been observed. For this analysis, only the rejection of null hypothesis of no efficacy was considered for both questions; the nominal significance level for rejecting H0 was taken as 0.0084. To compensate for this interim look, 11 additional events were needed for the final analysis (534 instead of 523).

Primary analysis was on the intention-to-treat population defined as all randomized patients in the arm they were allocated to by randomization. Relative dose intensity (RDI) was calculated as the administered dose per time as delivered divided by the planned dose per planned time of delivery. In 2011, the study was amended to include a prospective analysis of the efficacy results in relation to tumor IDH status and to allow iMRT after additional quality control for treatment delivery.

Support and study analysis

Schering Plough/Merck supported the study by an unrestricted grant and by the provision of temozolomide but had no role in the data collection, analysis, interpretation, writing of the manuscript or the decisions to submit . The study protocol was prepared by EORTC, the study database was developed, housed and analyzed by EORTC. TG, MvdB, BB and MW had access to all data. All authors have reviewed and approved of the manuscript. No writing assistance was provided. AN, TG, BB and MvdB had the responsibility for the submission of the manuscript.

Results

Between December 4, 2007 and September 19, 2015 1407 patients were screened and 748 were randomized. The required number of events for the interim analysis was observed in May 2015. This report is based on all data up to May 31, 2015 (clinical cut-off date for the interim analysis), with a first database lock on August 31, 2015 for the report to the IDMC, and a second lock for the study report on May 12 2016. At the time of the clinical cut-off date, 1400 patients had been registered and 745 randomized by 137 institutions in 12 countries (Figure 1). No significant imbalances in baseline characteristics were observed between the four treatment arms (Table 1). MGMT methylation status was available for 275 of 745 (37%) patients at randomization and for 550 of 745 (74%) patients at the time of the interim analysis.

Treatment

All patients were treated according to the arm to which they were randomized. All except sixteen patients completed radiotherapy. Thirty patients did not start adjuvant treatment (figure 1), 21 of the 188 patients randomized to radiotherapy with concurrent temozolomide and 9 of the 185 patients to radiotherapy alone. RDI of concurrent temozolomide was more than 90% in 89% (312 349) of patients with sufficient treatment information available. The RDI in patients who completed adjuvant temozolomide was 92%; in 12% (31/262) of patients the RDI was below 70%. Sixty-four percent (167/262) of patients who completed adjuvant temozolomide had at least one cycle delayed: 28% (74) for hematological toxicity, 6% (16) for non-hematological toxicity, 3% (8) for both and 47% (123) for non-drug related reasons.

Toxicity

Treatment was generally well tolerated. The most frequent related toxicity was hematological (supplemental table 1), with 8-12% of patients in the temozolomide-containing arms experiencing grade 3 or 4 toxicities, most frequently thrombocytopenia (7–9%). Supplemental table 1 summarizes the most frequent non-hematological grade 3 and 4 toxicities, excluding neurological events. Apart from constitutional and gastrointestinal toxicities, most toxicities were judged unrelated. Grade 3 or 4 increase in transaminases occurred in 1% of temozolomide treated patients (5:547).

Efficacy outcomes

With a median follow-up of 27 months, 344 patients (46%) had progressed and 221 patients (30%) had died: 129 in the arms without adjuvant temozolomide and 92 in the adjuvant temozolomide arms. The HR [99.145 CI] for the primary endpoint of OS adjusted for stratification factors for the arms containing adjuvant temozolomide was 0.65 [0.45, 0.93] (Table 2). Figure 2a shows the univariate OS analysis (HR 0.67, 95% CI 0.51, 0.88). If the methylation status of tumors that became known after randomization are also considered, the HR [99.145 CI] for adjuvant temozolomide was 0.651 [0.454, 0.934]. Age (under 50 or 50 years and older) was also a highly significant risk factor for survival (HR 4.0, [2.8, 5.7]). In univariate analysis, PFS was also superior in patients receiving adjuvant temozolomide (Figure 2b, HR 0.62, 95% CI 0.50, 0.76]). Table 3 shows additional median and 5 year PFS and OS analyses.

Treatment at progression

In the non-adjuvant arms, 200 patients progressed, compared with 144 in the adjuvant arms. Details for treatment given at progression were available for 195 and 143 patents respectively (supplemental table 2). Of these 338 patients, 303 received some additional treatment, mostly chemotherapy. Any chemotherapy was given to 143 (73%) in the non-adjuvant and 89 (62%) in the adjuvant arm, with temozolomide or PCV chemotherapy respectively being given to 82 (42.1%) and 19 (9.7%) in the non-adjuvant arms, and 31 (21.7%) and 20 (14.0%) in the adjuvant arms. Bevacizumab was administered to 44 patients (22.6%) in the non-adjuvant arms and 38 (26.6%) in the adjuvant arms. (Radio)surgery was used in 18 (9%) of the non-adjuvant arm patients and 9 (6%) of the adjuvant arm patients.

Discussion

This planned interim analysis of the CATNON trial showed a statistically significant and clinically meaningful benefit of adjuvant temozolomide on OS and PFS in non-co-deleted anaplastic glioma, mandating immediate release of the results. With adjuvant temozolomide, median PFS increased from 19 to 42.8 months and five-year OS increased from 44% to 56% . The present data do not imply that concurrent temozolomide does not have a beneficial effect; they only indicate that the interim analysis for this comparison did not cross the predefined boundaries. Of note, with 30% of patients having died and 46% having progressed, follow-up Is still immature and further follow-up is ongoing. Nevertheless, the HR observed in the interim analysis is striking, and passing the very strict statistical boundaries of the preplanned analysis.. With longer follow-up the survival curves diverge more , suggesting that with time the OS improvement is likely to increase. More follow-up is needed for both the answer to the concurrent question and for a more detailed OS analysis.

This trial on a molecularly defined subgroup of anaplastic glioma is noteworthy for several reasons. By allowing only patients without co-deletion of 1p/19q, this is the first trial on glioma which used molecular criteria for eligibility. This approach was induced by the worse outcome of 1p/19q non-co-deleted tumors in the PCV trials on anaplastic oligodendroglioma.3;4 It is also the first trial in WHO grade II or III glioma with a radiotherapy only group that investigated the addition of temozolomide, rather than PCV, to radiotherapy.15-17 The toxicity profiles of PCV and single agent nitrosoureas are less favorable than that of temozolomide.18;19As a consequence, temozolomide has almost completely replaced PCV in clinical use. However, until now there has been no evidence supporting the activity temozolomide in the adjuvant setting in diffuse grade II or III glioma; the pivotal temozolomide trial investigated glioblastoma which represents at the molecular level an entirely different disease with as a rule no IDH mutations.1 Although CATNON recruited patients with a less chemotherapy sensitive subset of anaplastic glioma compared to 1p/19q co-deleted glioma, temozolomide is clearly beneficial. Thirdly, prolonged follow-up was required to show an OS benefit in trials of adjuvant PCV in low grade glioma and anaplastic oligodendroglioma, with all three trials showing separation of survival curves only four to six years after randomization.[15-17] Each of these trials was initially reported as negative for OS, before the impact of early adjuvant PCV on OS was demonstrated with longer follow-up. Strikingly, in the CATNON trial there is an early separation of the OS curves which was sufficiently large to be detected in the interim analysis

By recruiting only patients without co-deletion of 1p/19q, this trial aimed at a molecularly defined subgroup of glioma patients ; since then further molecular research has resulted in new basic insight in glioma. In 2008, key mutations were first identified in IDH1 and IDH2 genes, occurring in 70-80% of all grade II and III diffuse glioma. These mutations are associated with improved outcomes and are now the cornerstone of the WHO 2016 classification of glioma.[20-24] In 2011 the study protocol was therefore amended to incorporate analyses of IDH mutation status; these molecular analyses of their predictive value for temozolomide efficacy are pending. In view of today's emphasis on IDH mutations and the large metabolic differences between IDHmt and IDHwt tumors, future trials in grade II and III glioma should consider only either IDHmt or IDHwt tumors.

The results of MGMT testing were not available for 60% of patients at the time of randomization, due to timelines issues with samples requiring both 1p/19q testing and MGMT testing in a limited timeframe. However, when considering the MGMT tests that became available post-randomization the study arms remained well balanced for MGMT promoter methylation. We also note that the percentage of successfully tested tumors showing MGMT methylation (42%) is lower than anticipated, being within the range expected in glioblastoma. This may be explained by the use in this trial of a PCR technique which was optimized for glioblastoma.[8;25] To overcome both this technical issue and the still modest rate of successful MGMT determination, MGMT promoter methylation status testing will be repeated using a genome wide methylation platform.[26;27] Both the presence of IDH mutations and MGMT promoter methylation have been proposed as predictive factors for benefit to chemotherapy. 28 The results of this study that will have enrolled both patients with IDH mutant and with IDH wild type gliomas with an anticipated difference in prognosis and sensitivity to outcome will help to decide on this question.

The interim analysis of the CATNON trial has shown a similar risk reduction (HR 0.65) in non-co-deleted anaplastic glioma treated with adjuvant temozolomide to that from adjuvant PCV in the low grade glioma trial, with an overall HR of 0.59, and HR 0.73 for the subset of astrocytoma (less likely 1p/19q co-deleted).17 Since the distinction between WHO grade II and III diffuse glioma is subjective and gradual and these tumors have similar molecular abnormalities, it seems reasonable to consider adjuvant temozolomide for patients with grade II non-co-deleted diffuse glioma. Furthermore, four trials now show clear clinical benefits from adding chemotherapy to radiotherapy, whereas two trials in grade II and III glioma failed to show improved outcome with initial chemotherapy alone compared to initial radiotherapy alone.15-17;29;30 With the currently available data, it seems prudent to extrapolate that treatment with chemotherapy alone will deliver worse OS results compared to initial treatment with radiotherapy and adjuvant chemotherapy. Another issue relates to the use of 12 cycles adjuvant treatment in this trial, whereas for glioblastoma 6 cycles of adjuvant temozolomide are advised. This duration of 12 cycles was chosen as half of the patients randomized to the adjuvant arm would not receive concurrent TMZ, and we specifically wanted sufficient TMZ exposure in the patients treated with TMZ in adjuvant setting alone. Lastly, the role of concurrent temozolomide remains to be clarified, at present no evidence based guidance can be given on this part of the treatment. While concurrent chemo-irradiation with temozolomide improves outcome in glioblastoma, outcome data on the individual parts of combined treatment (concurrent and adjuvant) in glioblastoma are lacking.1 Also, as opposed to the 12 months of adjuvant treatment in the CATNON trial, the pivotal glioblastoma trial used only 6 months adjuvant treatment. Of note, the use of concurrent temozolomide with radiation therapy may increase late neurotoxicity, which will especially be relevant in favorable prognosis patients.

To conclude, the preplanned interim analysis of the CATNON trial shows that 12 cycles of adjuvant temozolomide given after radiotherapy significantly improves OS in 1p/19q non-co-deleted anaplastic glioma and should now constitute standard care. Further follow-up and tissue studies are required to establish the efficacy of concurrent temozolomide chemotherapy and the impact of the molecular signature on outcome.

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Contibutions

The study was designed by MVDB, BB, SCE, MAV, AAB, PC, WM, MW, RS, KA,HJD, WNMD, TG, WW. The data were analyzed and the manuscripts was prepared by MVDB, BB, SE, AAB, AKN, WT, MW, HJD, WNMD, PW, VG, TG, WW, JMK. All authors provided administrative support and contributed to the data collection, and approval of the final version of the manuscript.

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Table 1. Patient characteristics at the time of randomization, including the stratification factors (bolded).

	Treatment arm				
	RT (N=187) N (%)	**TMZ/RT (N=185) N (%)**	**RT->TMZ (N=185) N (%)**	**TMZ/RT->TMZ (N=188) N (%)**	**Total (N=745) N (%)**
Age (years)					
Median	42.2	43.2	39.9	42.8	42.2
Range	19.0 - 81.2	20.1 - 77.1	20.0 - 82.3	18.3 - 80.1	18.3 - 82.3
≤50 years	132 (71)	124 (67)	129 (70)	129 (69)	514 (69)
>50 years	55 (29)	61 (33)	56 (30)	59 (31)	231 (31)
Presence of oligodendroglial elements (Yes vs No)					
No oligo	144 (77)	141 (76)	143 (77)	144 (77)	572 (77)
Oligo	43 (23)	44 (24)	42 (23)	44 (23)	173 (23)
WHO Performance Status (>0 vs 0)					
PS 0	110 (59)	109 (59)	108 (58)	112 (60)	439 (59)
PS >0	77 (41)	76 (41)	77 (42)	76 (40)	306 (41)
Presence of 1p LOH (Yes vs No)					
1p no loss	173 (93)	173 (94)	171 (92)	175 (93)	692 (93)
1p loss	14 (8)	12 (7)	14 (8)	13 (7)	53 (7)
Pre-randomization MGMT (Methylated vs Unmethylated vs Undetermined/invalid)					
Methylated	29 (16)	27 (14.6)	29 (16)	29 (15)	114 (15)
Unmethylated	40 (21)	40 (21.6)	40 (22)	41 (22)	161 (22)
Undetermined/invalid	118 (63)	118 (63.8)	116 (63)	118 (63)	470 (63)
Post-randomization MGMT (Methylated vs Unmethylated vs Undetermined/invalid)					
Methylated	60 (32)	53 (29)	66 (36)	54 (29)	233 (31)
Unmethylated	80 (43)	76 (41)	76 (41)	85 (45)	317 (43)
Undetermined/invalid	47 (25)	56 (30)	43 (23)	49 (26)	195 (26)

	Treatment arm				
	RT	**TMZ/RT**	**RT->TMZ**	**TMZ/RT->TMZ**	**Total**
	(N=187)	**(N=185)**	**(N=185)**	**(N=188)**	**(N=745)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Sex					
male	107 (57)	116 (63)	102 (55)	102 (54)	427 (57)
female	74 (40)	65 (35)	79 (43)	79 (42)	297 (40)
Missing	6 (3)	4 (2)	4 (2)	7 (4)	21 (3)
Mini Mental State Evaluation					
Median	29	30	30	29	29
<27	25 (13)	21 (11)	21 (11)	24 (13)	91 (12)
≥27	138 (74)	150 (81)	145 (78)	146 (78)	579 (78)
Missing	24 (13)	14 (8)	19 (10)	18 (10)	75 (10)
On corticosteroids at study entry					
no	131 (70)	128 (69)	128 (69)	122 (65)	509 (68)
yes	49 (26)	54 (29)	52 (28)	58 (31)	213 (29)
Missing/unknown	7 (4)	3 (2)	5 (3)	8 (4)	23 (3)
Prior surgery for low grade tumor					
no	158 (85)	161 (87)	160 (87)	154 (82)	633 (85)
yes	23 (12)	20 (11)	21 (11)	27 (14)	91 (12)
Missing	6 (3)	4 (2)	4 (2.2)	7 (4)	21 (3)
Type of surgery					
biopsy	33 (18)	41 (22)	35 (19)	40 (21)	149 (20)
partial removal	100 (54)	86 (47)	89 (48)	72 (38)	347 (47)
total removal	48 (26)	54 (29)	57 (31)	69 (37)	228 (31)

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Table 2. Cox model of the primary endpoint, with the effect of adjuvant temozolomide adjusted by the stratification factors (and MGMT status at randomization).

Parameter	**Pr > ChiSq**	**Hazard Ratio (HR)**	**99.145% HR Confidence Limits**
Adjuvant Temozolomide	**0.0014**	**0.65**	**0.450, 0.926**
Age (>50 vs ≤50)	<.0001	4.04	2.784, 5.867
WHO Performance Status (>0 vs 0)	0.0273	1.36	0.943, 1.960
Presence of 1p LOH (Yes vs No)	0.0572	1.56	0.844, 2.877
Presence of oligodendroglial elements (Yes vs No)	0.2230	1.20	0.812, 1.762
MGMT (Methylated vs Unmethylated)	0.0031	0.49	0.259, 0.925
MGMT (Undetermined/invalid vs Unmethylated	0.1606	0.81	0.538, 1.207

77 3. Median (months) and 5-year OS and PFS (percentage) with 95% CI

	Progression Free survival			**Overall Survival**		
Adjuvant TMZ	Events	Median (months)	% at 5-years	Events	Median (months)	% alive at 5-years
No	200	19.0 (14.4, 24.6)	24.3 (17.7, 31.6)	129	41.10 (36.6, 60.7)	44.1 (36.3, 51.6)
Yes	144	42.8 (28.6, 60.6)	43.1 (35.0, 50.9)	92	Not reached	55.9 (47.2, 63.8)

Figure 1: CONSORT diagram at the time of interim analysis

Figure 2 a, b. Overall survival (a) and Progression Free Survival (b) in patients treated with or without adjuvant temozolomide chemotherapy

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